Exp Mail EV335394329US
USAN 10/698,955

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
A61K 9/127, 45/05

A1

(11) International Publication Number: WO 92/08448

(43) International Publication Date: 29 May 1992 (29.05.92)

(21) International Application Number: PCT/US91/08185

(22) International Filing Date: 4 November 1991 (04.11.91)

(30) Priority data:
611,170 9 November 1990 (09.11.90) US

(71) Applicant: CELL TECHNOLOGY, INC. [US/US]; 1668 Valtec Lane, Boulder, CO 80301 (US).

(72) Inventors: McCALL, Catherine, Anne ; 709 Pleasant Street, Boulder, CO 80302 (US). PEARSON, Frederick, C. ; 5640 Old Stage Road, Boulder, CO 80302 (US).

(74) Agents: McCUBBREY, J., Bruce et al.; McCubbrey, Bartels, Meyer & Ward, Suite 2700, One Post Street, San Francisco, CA 94104-5231 (US).

(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent).

Published
With international search report.

(54) Title: METHOD FOR PREVENTING DRUG-INDUCED OR RADIATION MYELOSUPPRESSION

(57) Abstract

A method is described for treating a patient undergoing therapy by radiation or by a drug which induces myelosuppression. The patient is administered a therapeutically effective amount of a biological response modifier comprising two major particle populations, one such population being of lesser size particles comprised of ribosomes and the other such population being comprised of natural membrane vesicles, in a suspending buffer. The membrane vesicles and ribosomes are endogenous to a selected microorganism which is substantially non-pathogenic in humans. The biologic response modifier is substantially free of intact cells, and has tolerable levels of endotoxin, cell walls, and cell membrane fragments.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MG	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MN	Mongolia
BE	Belgium	GA	Gabon	MR	Mauritania
BF	Burkina Faso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GN	Guinea	NL	Netherlands
BJ	Benin	GR	Greece	NO	Norway
BR	Brazil	HU	Hungary	PL	Poland
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland	KR	Republic of Korea	SN	Senegal
CI	Côte d'Ivoire	LI	Liechtenstein	SU+	Soviet Union
CM	Cameroon	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TG	Togo
DE*	Germany	MC	Monaco	US	United States of America
DK	Denmark				

\+ Any designation of "SU" has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.

METHOD FOR PREVENTING DRUG-INDUCED OR RADIATION MYELOSUPPRESSION

This invention relates to the prevention of myelosuppression in patients undergoing treatment with radiation or chemotherapeutic agents and the like. More particularly, the invention relates to the use of a non-specific biological response modifier for improving the ability of such patients to resist opportunistic infections.

BACKGROUND OF THE INVENTION

Chemotherapy and radiotherapy are two of the most successful treatment modalities for cancer. However, both have effects on normal cells as well as malignant ones, and hence give rise to a variety of undesirable side effects. The primary life threatening side effect is myelosuppression - a loss of production of the granulocytic and monocytic leukocyte cell lines. These cell lines act as the first line of defense against pathogens such as bacteria and viruses. Patients experiencing chemo or radiotherapy-induced myelosuppression are prone to infection with opportunistic microorganisms. These infections can be lethal, and are one of the most common dose-limiting toxicities of cancer therapy. This, in turn, lowers the efficacy of the therapy, in that the level of tumor cell kill is roughly proportional to the amount of radiation or drug administered.

Chemotherapeutic drugs and radiation produce both tumor cell kill and myelosuppression by interfering with cell division. This can occur by direct damage to DNA, by activation of DNA modifying enzymes or production of reactive molecules such as superoxide, which in turn damage DNA, or by interfering with the mitotic spindle which mechanically separates chromosomal material during cell division. Tumors will be disproportionately

affected, as their growth fraction will contain a high percentage of cells which are dividing, or are about to divide. However, normal tissues which have a high turnover rate, such as epithelium (skin and gut lining) and the hematopoetic system (blood components) are also adversely affected. Blood leukocytes such as the polymorphonuclear cells mainly responsible for engulfing pathogens are very short-lived cells - their life span being measured in hours after they are produced in the bone marrow. Chemotherapy and radiation kill the rapidly dividing precursors of these cells, and hence myelosuppression is evident shortly after treatment. The mechanism for production of myelosuppression by chemo or radiotherapy is thus different to the mechanism operative in burns and trauma patients, where the myeloid precursors are not killed but rather downregulated in some as yet undefined fashion.

Radiation affects cells by the production of chemically active intermediates - free radicals - which damage DNA, thus rendering the cell unable to divide. Different lineages of cells are different in their ability to withstand radiation damage. Cells with a slow turnover rate (e.g. muscle) are less radiosensitive than cells with a high turnover rate (e.g. epithelium). Some cells which are radio resistant have more effective DNA repair systems, or can 'scavenge' radiation induced reactive intermediates before they can damage DNA.

Chemotherapeutic agents can be divided into groups depending on their origin and mode of action. Examples of the various subgroups, all of which can be myelosuppressive, are given below:

Antimetabolities:

These compounds mimic intermediates in several required synthetic processes in the cell which lead to productio of DNA precursor molecules - purines and pyrimidines.

Examples are methotrexate and cytosine arabinoside (ARA C)

Antibiotics:

Doxorubicin (Adriamycin) is an example of a very effective antitumor antibiotic drug derived from a fungus. The mechanism of action of this drug is unclea but seems to involve direct binding to DNA or productio of DNA damaging free radicals.

Alkylating agents:

These agents chemically interact with DNA forming covalent bonds with the molecule itself. This causes both misreading of the DNA and fragmentation of the DNA strands. Examples of effective alkylating drugs are cyclophosphamide and the nitrosoureas (BCNU).

Plant alkaloids:

Several compounds derived from plants (Vinca alkaloids vincristine and vinblastine) bind to the tubulin molecule which is the subunit of the mitotic spindle. Physical separation of chromosomes at cell division is thus prevented and cell death ensues.

In order to prevent opportunistic infections in patients undergoing drug or radiation therapy, several approaches have been employed. Although in some cases, antibiotics are effective many individuals may still be infected with opportunistic bacteria, viruses or fungi, because resistant strains of pathogens have rapidly arisen. Another therapeutic approach for such patients is to attempt to reverse the attendant immunosuppression, so that the patient's own immune system can counter-attack the invading microorganisms.

The use of highly purified single agents with apparently clearly defined biological activities, such as the colony-stimulating factors (e.g. GM-CSF) interleukin I, interleukin II, and tumor necrosis factor, appears to have potential in restoring some specific white cell

production or immune functions. However, experience in cancer therapy has shown that the administration of unphysiologically large doses of cytokines such as interleukin-2 sets off an as yet ill-defined cascade of other cytokines which can lead to unexpected effects including considerable toxicity. The proliferation, maturation and function of hematopoietic cells is under the control of a complex series of interacting mediators (1). Thus, optimal use of single agents such as cytokines will almost certainly require combination therapy consisting of the timed administration of multiple factors in a sequence designed to mimic normal hematopoiesis.

Other prior art studies of immunomodulators have used broad acting "non-specific" agents such as Corynebacterium parvum, Bacillus Calmette Guerin (BCG) and levamisole. Non-specific immunomodulatory agents, although indicating some promise, have drawbacks which could limit their use and/or effectiveness in many patients. Often, bacterially derived agents such as C. parvum and BCG are difficult to purify, vary in their potency from lot to lot, have a short shelf-life, and have undesirable side affects, particularly those patients already weakened by chemo or radiotherapy.

A new biologic response modifier (BRM), manufactured by Cell Technology, Inc. (CTI) of Boulder, Colorado has been shown to be an effective immunomodulator for treating some types of cancers. The absence of substantial toxicity along with product consistency and the ability to lypholize this BRM make it an attractive product for clinical use. However, it is not apparent or predictable that this material would have a therapeutically significant biological affect with respect to immune-suppressed drug or radiation therapy patients.

It is an object of the present invention to

provide an improved method for preventing immunosuppression in patients undergoing radiation or drug therapy.

Another object of the invention is to provide an improved treatment for patients undergoing drug or radiation therapy to enhance resistance to opportunistic infections.

A further object of the invention is to provide an improved non-specific biological response modifier for improving the ability of certain immune-compromised patients to resist opportunistic infections.

Other objects of the invention will become apparent to those skilled in the art from the following description, taken in connection with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a set of graphs illustrating the effects of various doses of a cytotoxic agent (cyclophosphamide) with or without CTI-BRM, on spleen white blood cell progenitors in the mouse.

Figure 2 is a bar graph illustrating total white blood cel (WCC) and granulocyte levels in rats treated with a cytotoxic agent (cytosine-arabinoside, ARA-C) and CTI-BRM.

Figure 3 illustrates white blood cell counts in dogs treated with a cytotoxic agent (adriamycin) and different dosages of CTI-BRM.

SUMMARY OF THE INVENTION

Very generally, the invention comprises a method for treating a patient, undergoing therapy by radiation or by a drug which induces myelosuppression, in order to enhance the ability of the patient's immune system to resist opportunistic infection. A therapeutically effective amount of a non-specific biological response modifier is administered to the patient. The biological response modifier comprises natural membrane vesicles and

ribosomes, in a suspending buffer. Preferably, the ribosomes and vesicles are both derived from the bacterium Serratia marcescens.

DEFINITIONS

For the purpose of preciseness, the following terms used in this specification and the appended claims are defined:

"Non-toxic" means within a level of toxicity which is tolerable by the mammalian host receiving biologic response modifier therapy.

"Non-immunogenic" means evoking a sufficiently low immunogenic response, or no response at all, such that undesired, chronic inflammatory and hypersensitivity responses are not elicited, significantly, in the mammalian host.

"Mean diameter" means the mean diameter of MSD Particle Size Distribution Analysis as measured on a BI-90 (Brookhaven Instrument Corp.) particle sizer. The measurement involves an intensity weighting of the size averaging process and is explained more fully in the Operator's Manual for the instrument, Chapter 6, incorporated herein by reference.

"Substantially non-pathogenic in humans" means not or rarely associated with disease in humans of normal health. Since most microorganisms are capable of causing opportunistic infections under the right circumstances, such as in persons whose immune system has been compromised, this definition excludes only those organism which typically cause non-opportunistic infections.

"Tolerable level of endotoxin, cell walls, and cell membrane fragments" means that any such fractions, if present, have a low enough level of biologic activity to maintain a relatively non-toxic characteristic as defined herein.

"Immune suppressing response" means an immune response which so attenuates the effect of the desired

immune response as to be unacceptable for medical purposes.

"Natural membrane vesicles" means membrane vesicles prepared from membranes which are derived from living or dead natural cells.

DETAILED DESCRIPTION OF THE INVENTION

The non-specific biological response modifier employed in the method of the invention, and its method of manufacture, are described in detail in co-pending application U.S. Serial No. 057,344. A corresponding application has been published under the Patent Cooperation Treaty in PCT Application PCT/US87/01397. A full and complete description of the biological response modifier and its method for manufacture is contained in those applications sufficient to enable a person having ordinary skill in the art to reproduce the subject material.

For the purposes of this application including the appended claims, the expression "CTI-BRM" shall mean the biological response modifier described and claimed in the foregoing application.

CTI-BRM is, at the time of filing this application, undergoing Phase II Clinical Trials for cancer pursuant to regulations of the Food and Drug Administration of the United States of America. Information relating to therapeutically effective amounts of CTI-BRM has been generated in those trials and some of this information is contained in PCT Application No. PCT/US87/01397, as well as in other published articles.

For the purposes of this application, a therapeutically effective amount of CTI-BRM is considered to be substantially equivalent to the amount found to be therapeutically effective in connection with cancer, as set out in the above-mentioned PCT patent application and other publications. However, additional variants of therapeutically effective amounts may be readily

determinable by the treating physician through observation, and from the information provided herein. Such are intended to be encompassed within the scope of term "therapeutically effective amount" as used herein and in the appended claims.

Specifically, CTI-BRM comprises natural membrane vesicles and ribosomes in a suspending buffer. The vesicles are comprised of cellular membrane material and are endogenous to a selected organism. The ribosomes are also endogenous to the selected organism. The biologic response modifier is substantially free of intact cells, cell walls, and cell membrane fragments. The selected organism is one which does not evoke an immune suppressing response, is non-pathogenic in humans, and is one from which membrane vesicles are capable of being formed from cell membrane material and which vesicles are readily endocytosed by the monocyte macrophage cell line. The vesicle population of the CTI-BRM exhibits a mean diameter of at least 180nm on particle size analysis.

Further description of the CTI-BRM is provided in the aforementioned published PCT application. Such description, and the method of preparation, are set forth with particularity in that application and are incorporated herein by reference. The ability of CTI-BRM to alter the levels of various white blood count and neutrophil levels in cancer patients is described in the aforementioned PCT published application.

Dosage regimens described in the aforementioned published PCT patent application included dosage levels ranging from .25 to 10 milligrams administered from 3 to 6 times spaced at 7 day intervals and administered subcutaneously. Toxicity trials indicated no significant toxicity problems with those dosage regimens and further indicated that the product was well tolerated by the human patients. Adjuvant arthritis, granulomas, ulcerations, and similar effects of toxic components are

minimized or eliminated by the use of the CTI-BRM.

A preferred source of the material for the CTI-BRM is the organism Serratia marcescens. However, other organisms are suitable as a source for the membrane vesicles and ribosomes utilized in the CTI-BRM. Such microorganism should not be a member of the microflora of the patient. Moreover, the microorganisms common bacterial antigen must not react or at least must be poorly cross-reactive with organisms making up the normal microflora of the patient. Examples of suitable microorganism sources other than Serratia marcescens are Erwinia chrysanthemi (pectobacterium) and Enterobacter aerogenes.

In manufacturing the CTI-BRM, bacterial cells of a strain of microorganism which is not present in the microflora of the patient to be treated and which has a common bacterial antigen which does not cross react or is poorly cross reactive with organisms making up the normal microflora of the patient to be treated, are cultivated. The cultivated cells are harvested and cell membrane is disassociated with an appropriate detergent. The cellular concentrate is subjected to disruption mechanically at a pressure in excess of 10,000 psi to produce membrane vesicles with a mean diameter not less than 180 nm. The membrane vesicles and free ribosomes are separated from the remaining cellular material in the cellular lysate. The membrane vesicles and free ribosomes are then re-suspended in an appropriate buffer.

CTI-BRM is a powerful immunomodulator: it is rapidly phagocytosed by monocytes/macrophages which then show increased phagocytic, bactericidal and tumoricidal activity. (2) Patients injected subcutaneously with CTI-BRM show significant rises in granulocyte counts 24 hours later. (3) stimulation of human peripheral blood mononuclear cells with CTI BRM results in elevation of NK activity (4), increased T-cell mediated cytotoxicity, and

augmented lymphocyte and monocyte antibody mediated cytotoxicity (ADCC) (5). The enhancement of these cellular effector functions is most likely a result of a cascade of cytokine release which occurs after CTI-BRM stimulation. Supernatants from CTI-BRM stimulated human peripheral blood mononuclear cells contain Il-1, Il-6, interferons alpha and gamma, TNF and GM-CSF. Both human and rat CTI-BRM stimulated monocytes produce substantial quantities of a myeloid differentiation factor, as measured by the ability to induce differentiation of the rat C51 choloroleukemia in vitro and in vivo.(6)

This ability of CTI-BRM to stimulate endogenous production of cytokines, inducing proliferation, maturation or enhancement of function of macrophages and lymphocytes, suggests it may be useful for the treatment of radiation-induced or drug-induced myelosuppression. However, because such myelosuppression is a unique mechanism, it is by no means predictable that administration of CTI-BRM will work.

To test the efficacy of using ImuVert to rescue animals from drug-induced immunosuppression, CF-1 mice were treated with cyclophosphamide at two doses-a "low" dose of 150mg/kg amd a "high" dose of 300 mg/kg. Subsequently, the mice were given one dose of either 10ug CTI-BRM (low dose) or 100ug CTI-BRM (high dose) intraperitoneally. In the mouse, the spleen is the major site of hematopoiesis, particularly under conditions of stress. This differs from the situation in humans where bone marrow is the primary hematopoietic organ. In mice the degree of protection/rescue from immunosuppressive agents can be measured by the splenic CFUc (colony forming units) assay in soft agar. Spleens were harvested at days 1, 2, 4, and 7 post CTI-BRM treatment and assayed for CFUc.

As shown in the graphs of FIGURE 1, both high and low doses of cyclophosphamide suppress colony formation

through days 3 and 4 post treatment with a rebound from treatment occurring by Day 6. Low dose CTI-BRM stimulates CFUc formation as quickly as 24 hours post injection and maintains stimulation through day 4 with effects diminishing by day 6. High dose CTI-BRM has a longer lasting stimulatory effect, through day 6. At day 6, 100ug CTI-BRM mice have twice the number of CFUs than the 10ug dose animals.

Combination treatment of low dose cyclophosphamide and low dose CTI-BRM maintains CFUs at control values through day 3. Low dose Cyclophosphamide/high dose CTI-BRM stimulates CFU formation as early as 24 hours and at day 6 CFUc,s are higher than can accurately be measured in the assay. CTI-BRM can also mitigate the effects of high dose cyclophosphamide. High dose CTI-BRM takes 4 days to overcome the effects of high dose cyclophosphamide, but low dose CTI-BRM requires 6 days to exert its effects.

In conclusion, treatment of immunosuppressed mice with CTI-BRM accelerates their recovery as measured by spleen weight and by CFUc numbers. The clinical relevance of this observation is that CTI-BRM may be used to protect patients undergoing chemotherapy from infections resulting from low white cell counts, allowing higher, possibly more effective doses of chemotherapy to be given.

CTI-BRM also maintains peripheral blood leukocyte counts in two other animal models of drug-induced cytopenia:

1. <u>Cytosine arabinoside (ARA-C) treatment in rats</u> (see FIGURE 2). Adult rats were given 200 mg/kg ARA-C for 7 days. White cell counts were performed at day 15. It can be seen that ARA-C treated rats have lower total white cell counts and lower numbers of granulocytes than normal control animals. Rats treated with CTI-BRM (25ug/day for 7 days) at the same time as

ARA-C had granulocyte counts equivalent to normal controls.

2. Adriamycin treatment of dogs. Adult mongrel dogs (see FIGURE 3) weighing approximately 50lb were given adriamycin at 30mg/m^2 i.v. This produces a fall in blood cell counts, particularly neutrophil granulocytes, maximal 7 - 10 days after adriamycin therapy. If the animals are also given CTI-BRM at 0.04mg/kg twice weekly or 0.08 mg/kg 3 times weekly, the neutrophil counts recover faster, thus shortening the time the animals are neutropenic.

CTI-BRM has been shown to mitigate myelosuppression caused by drugs from three classes of chemotherapeutic agents, namely ARA-C, cyclophosphamide, and adriamycin. The mechanism of action of CTI-BRM in mitigating myelosuppression is not known, but probably is a result of production of endogenous cytokines and growth factors which speed division of remaining precursor cells and aid maturation of the myeloid cells.

Administration of the CTI-BRM pursuant to the method of the invention is capable of restoring the immune system in the case of patients suffering from myelosuppression caused by radiation or drugs. The method of the invention is safe in that it is well tolerated by patients. Restoration of the immune system in such patients restores their ability to withstand opportunistic infection, thereby greatly enhancing their chances for recovery.

Various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and accompanying illustrations. Such modifications are intended to fall within the scope of the appended claims.

LIST OF REFERENCES

1. Sieff CA. 1987. J. Clin. Invest. 79, 1549 - 1557

2. McCall C, Weimer L, Campbell P, Riches D, and Urban R. 1988. J. Cell Biochem. Suppl. 12E, 175.

3. Jaeckle K, Hil F. and Mittelman A. 1989. J. Oncol in Press

4. Warren RP, McCall CA, and Urban RW. 1989. Mol. Biother. 1, 145

5. Warren RP, McCall CA, and Urban RW. 1989. Mol. Biother. 1, 323

6. Jimenez JJ, McCall CA, Cirocco RE, and Yunis AA. 1989. J. Biol. Response Mod. 9 300-304.

WHAT IS CLAIMED IS:

1. A method for treating a patient undergoing therapy by radiation or by a drug which induces myelosuppression, comprising, administering a therapeutically effective amount of a biological response modifier comprising two major particle populations, one such population being of lesser size particles comprised of ribosomes and the other such population being comprised of natural membrane vesicles, in a suspending buffer, said membrane vesicles and ribosomes being endogenous to a selected microorganism which is substantially non-pathogenic in humans, said biologic response modifier being substantially free of intact cells, and having tolerable levels of endotoxin, cell walls, and cell membrane fragments.

2. The method of Claim 1 wherein said biological response modifier is derived from the microorganism Serratia marcescens.

3. The method of Claim 1 wherein said biological response modifier is administered subcutaneously.

4. The method of Claim 3 wherein said biological response modifier is administered at intervals from 2 to 7 days in an amount between about 0.25 mg and 10 mg.

5. The method of Claim 1 wherein said biological response modifier is administered intraperitonealy.

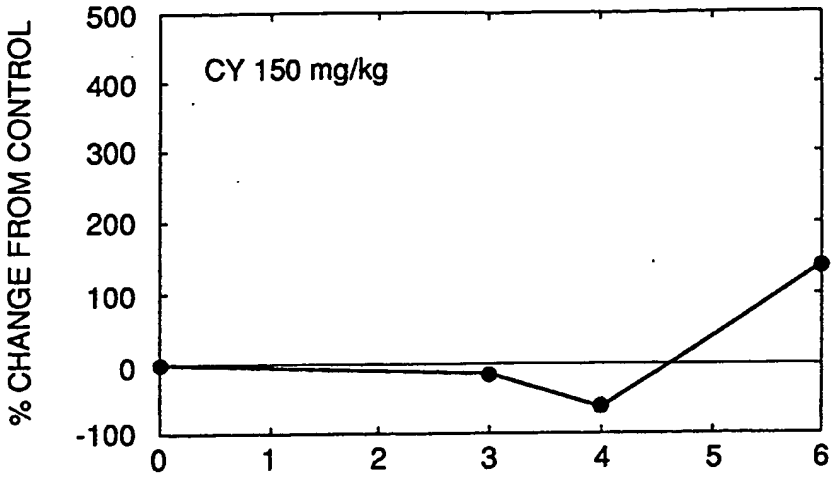

FIG._1A

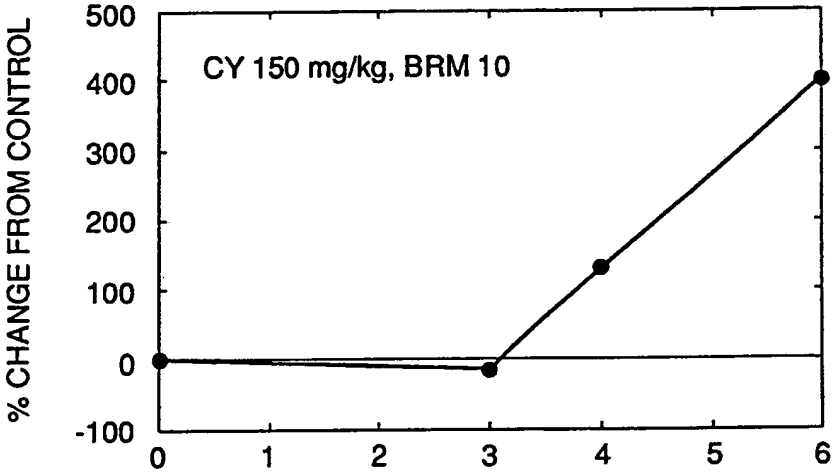

FIG._1B

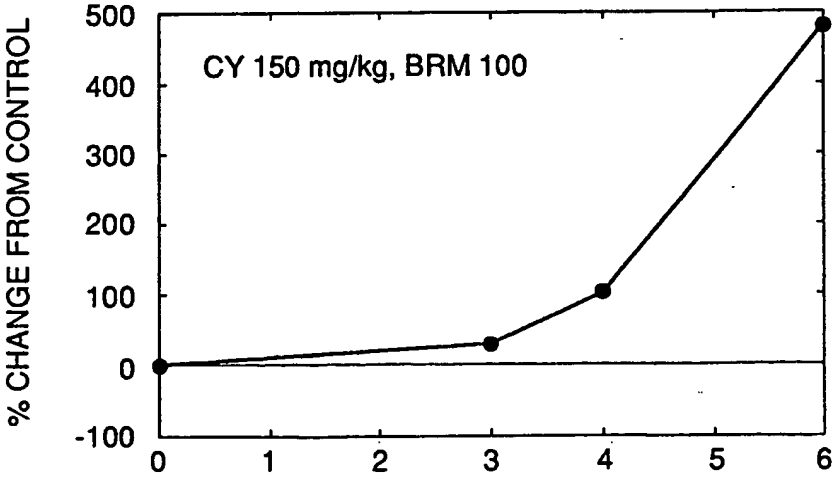

FIG._1C

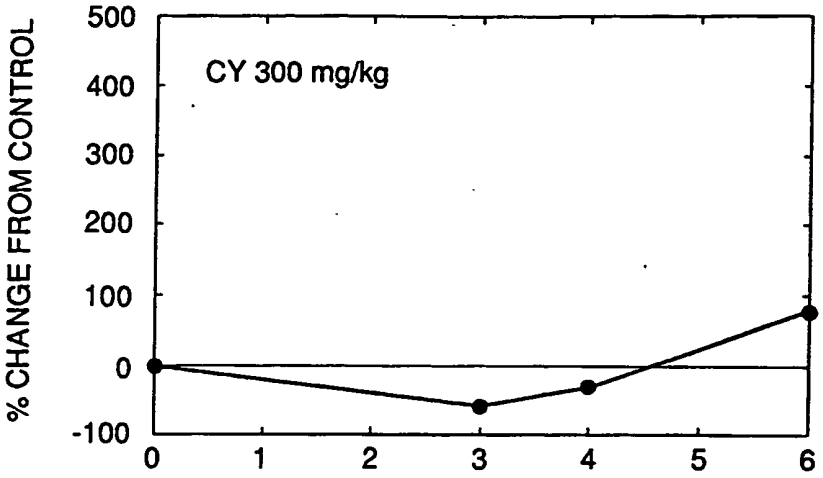

FIG._1D

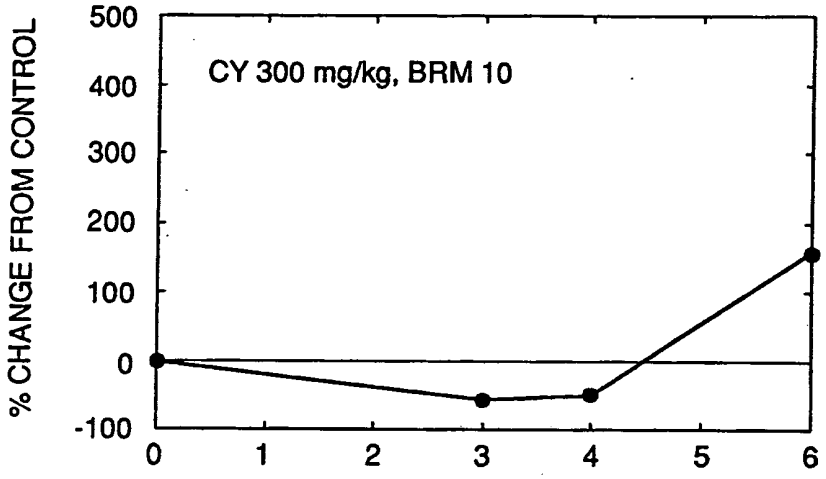

FIG._1E

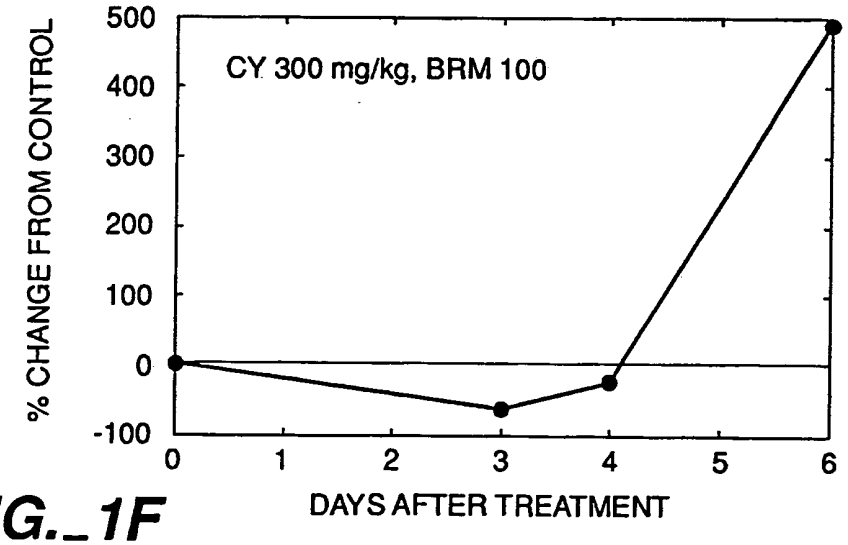

FIG._1F

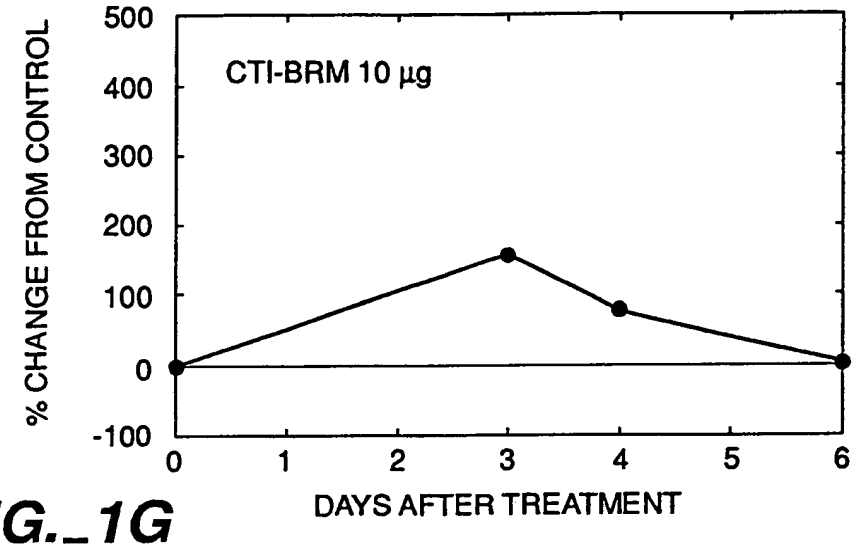
CTI-BRM 10 µg
% CHANGE FROM CONTROL
500
400
300
200
100
0
-100
0
1
2
3
4
5
6
DAYS AFTER TREATMENT

FIG._1G

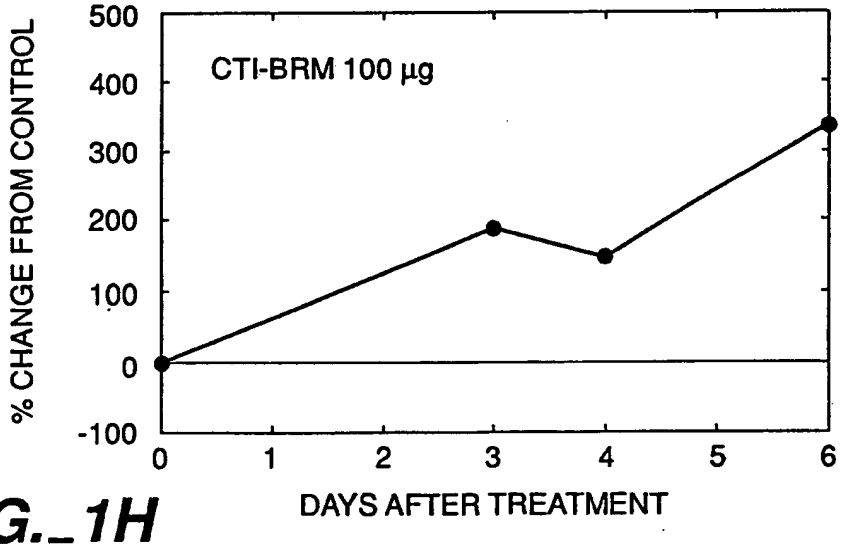
CTI-BRM 100 µg
% CHANGE FROM CONTROL
500
400
300
200
100
0
-100
0
1
2
3
4
5
6
DAYS AFTER TREATMENT

FIG._1H

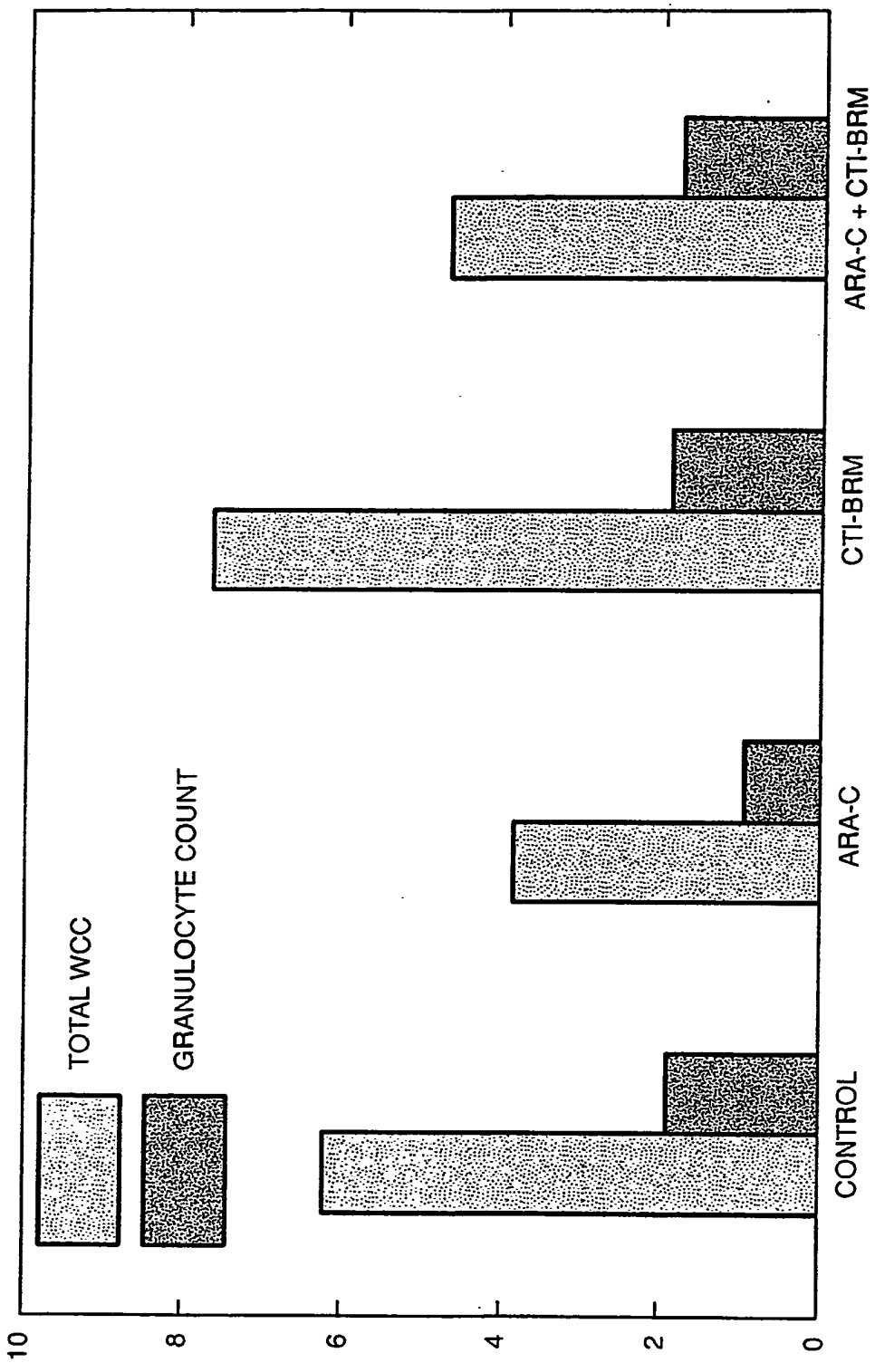
TOTAL WCC
GRANULOCYTE COUNT
CONTROL
ARA-C
CTI-BRM
ARA-C + CTI-BRM
TREATMENT GROUP
0
2
4
6
8
10
CELLS PER cu-mm (THOUSANDS)

FIG._2

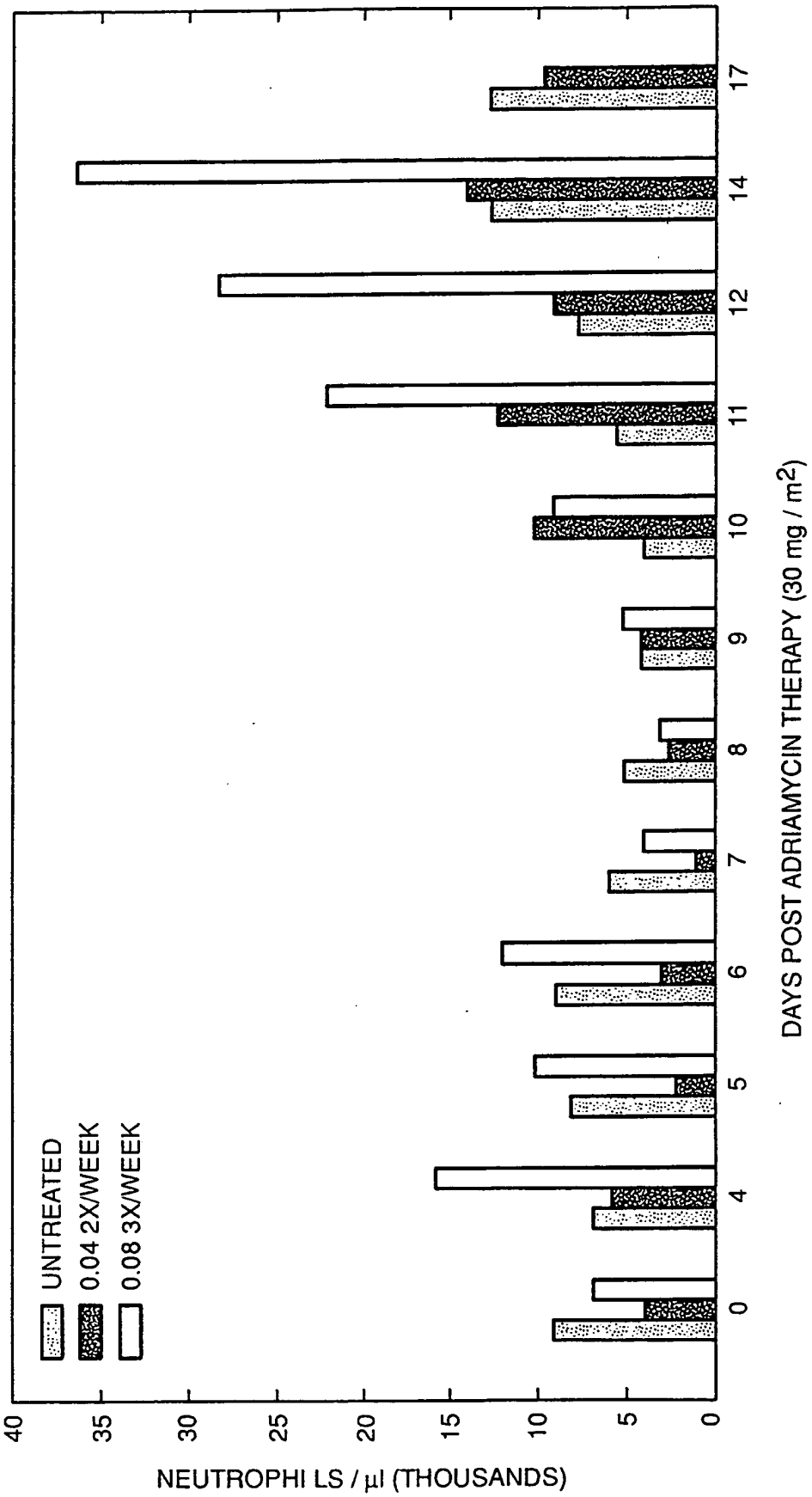
UNTREATED
0.04 2X/WEEK
0.08 3X/WEEK
NEUTROPHI LS / µl (THOUSANDS)
0
5
10
15
20
25
30
35
40
DAYS POST ADRIAMYCIN THERAPY (30 mg / m2)
0
4
5
6
7
8
9
10
11
12
14
17

FIG._3

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US91/08185

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

INT CL. (5): A61K 9/127; 45/05
U.S.CL : 424/450; 428/402.2; 514/885,889,974

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U. S. CL.	424/450; 428/402.2; 514/885,889,974.

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y, P	US, A, 4,971,801 URBAN 20 NOVEMBER 1990. See Figs 2 and 7-12; Col. 3, Line 62- Col. 4, Line 24; Col. 5, lines 3-21 and 33-44; Col. 7, Lines 3-24; Col. 11, lines 25-36; and Col. 14, Line 19- Col. 15, Line 49.	1-5
Y	US, A, 4,873,088 MAYHEW ET. AL. 10 OCTOBER 1989 See Abstract; Col. 4, lines 45-51; Col 5, lines 17-28; and Col. 8, Line 65-Col. 9, Line 36.	1-5
Y	US, A, 3,993,754 RAHMAN ET. AL. 23 NOVEMBER 1976 See Col. 2, lines 6-23; and Col. 5, Line 25- Col. 6, Line 7.	1-5
A	US, A, 4,053,585 ALLISON ET. AL. 11 OCTOBER 1977	1-5
A	US, A, 4,372,949 KODAMA ET. AL. 08 FEBRUARY 1983	1-5
A	US, A, 4,663,161 MANNINO ET. AL. 05 MAY 1987	1-5
A	US, A, 4,873,089 SCOTTO ET. AL. 10 OCTOBER 1989	1-5
A	JP, A, 58-49311 ELSAI KK 23 MARCH 1983	1-5

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
03 FEBRUARY 1992	13 FEB 1992

International Searching Authority	Signature of Authorized Officer
ISA/US	For RICHARD D. LOVERING

RECEIVED: RECOC-HO
INTERNATIONAL DIVISION

Form PCT/ISA/210 (second sheet) (Rev.11-87)